

Serial No.: 10/051,662

Our File No. 31140-B

AMENDMENTS

Please amend the application as follows:

IN THE SPECIFICATION:

At page 18, line 21, after "derivatives." insert:

--The pregnane progestins, derived from 17 alphahydroxy-progesterone, include, for example, medroxyprogesterone acetate, chlormadinone acetate, megestrol acetate, and cyproterone acetate. All of these are roughly 20% to 50% of the potency of norethindrone. The estranes, derived from 19-nortestosterone include norethindrone, norethynodrel, lynestrenol, norethindrone acetate, ethynodiol acetate, and norethindrone enanthate. All of these are metabolized to norethindrone and are roughly equivalent to the same dosage of norethindrone. The gonanes are derived from the basic estrane structure, with the addition of an ethyl group of position 13 of the molecule. This additional ethyl group confers augmented progestogenic activity, and also significant androgenic effects. Drugs in this group include, for example, norgestrel (-d and -1), norgestimate, desogestrel, and gestodene. All of these are roughly equivalent to four times the dose of norethindrone. A preferred progestin product is levonorgestrel or other 19-nortestosterone derivatives.--

At page 19, line 11, after "norethindrone." insert:

--Other progestin daily dosages are less than about 1.25 mg of norethindrone equivalent, or less than 0.5 mg daily of a norethindrone equivalent dose.--

At page 20, line 4, after "reference)." insert the following paragraphs:

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--Oral contraceptive administration regimens are selected to simulate the normal menstrual cycle, which averages 28 days in women of reproductive age. The menstrual cycle begins at the onset of a menstrual bleeding episode and lasts until the onset of the next. Thus, day 1 of a cycle would be the first day of menstruation, and day 28 would be the day before the onset of the next menstrual bleeding episode. Oral contraceptives are typically taken daily, at the same time each day, for 21 days, followed by a placebo for the next 7 days. The female generally experiences a menstrual bleeding episode during the seven-day placebo period. Thus, a woman first starting on oral contraceptives is generally instructed to begin taking them at some time between day 1 and 7.

The oral contraceptives must be taken according to the daily regimen for a full menstrual cycle before they are effective for contraception. A woman beginning an oral contraceptive regimen is not effectively protected against conception if the oral contraceptives are taken for less than the full menstrual cycle, if they are not taken daily, and if they are not taken for 21 consecutive days. A minimum blood level of the exogenously administered estrogen or progestin hormones must be maintained daily in order to suppress ovulation. If the blood level drops too low, ovulation may occur and the other inhibitory mechanisms on the reproductive tract may fail to prevent conception.

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Various combinations of progestin and estrogen that have been used in oral contraceptives are shown in Table 1.

TABLE 1

Previously Used Combinations of Progestin and Estrogen

<u>Progestin</u>	<u>Dose</u> (mg)	<u>Noreth-</u> <u>indrone</u> <u>Equivalent</u> <u>Dose</u>	<u>Estrogen</u>	<u>Dose</u> (mg)	<u>EE Equi-</u> <u>valent</u> <u>Dose</u> (mg)	<u>P/E Ratio</u>
Noreth-	9.85	9.85	Mestranol	0.150	0.105	93.810
	5.00	5.00		0.075	0.053	95.238
	2.50	2.50		0.036	0.025	99.206
	2.50	250		0.100	0.070	35.714
Noreth-	10.00	10.00	Mestranol	0.060	0.042	238.095
	2.00	2.00		0.100	0.070	28.571
	1.00	1.00		0.050	0.035	28.571
	1.00	1.00		0.080	0.056	17.857
Noreth-	1.00	1.00	Ethinyl estradiol	0.050	0.050	20.000
	0.50	0.50		0.035	0.035	14.286
	0.40	0.40		0.035	0.035	11.429
Noreth-	2.50	2.50	EE	0.050	0.050	50.000
	1.00	1.00		8050	0.050	20.000
	0.60	0.60		0.030	0.030	20.000
	1.50	1.50		0.030	0.030	50.000
	1.00	1.00		0.020	0.020	50.000
Ethyno-	1.00	1.00	Mestranol	0.100	0.070	14.286
diol diacetate						
Ethyno-	1.00	1.00	EE	0.050	0.050	20.000
diol diacetate						
dl-	0.50	2.00	EE	0.050	0.050	10.000
	0.30	1.20		0.030	0.030	10.000
Equivalencies						

50 mg Mestranol = 35 mg Ethinyl estradiol (EE)

0.5 mg dl-Norgestrel = 2 mg Norethindrone

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Each block describes a specific combination of progestin and estrogen, e.g., norethynodrel and mestranol, and within each block older combinations are listed first, with successively newer combinations following. Two trends are evident. First, over time the size and ratio of the dosages has decreased, i.e., the downward trend of the progestin component is steeper than the downward trend of the estrogen component. On a relative scale, therefore, estrogen has become more important over time. Second, with this downward trend in dosage, it is apparent that the relative ratio of progestin to estrogen is also trending downward. Oral contraceptives include triphasic preparations, an example of which has the following dosages: six days of 0.030 mg ethinyl estradiol +0.050 mg levonorgestrel, followed by 5 days of 0.040 mg ethinyl estradiol +0.075 mg levonorgestrel, followed by 10 days of 0.030 mg ethinyl estradiol +0.125 mg levonorgestrel, followed by 7 days of no contraceptive hormone treatment.—

At page 20, line 13, after "daily" insert:

--(equivalent to 10 to 20 mcg ethinyl estradiol orally per day)--

At page 20, line 20, after "therapy." insert:

--Other exemplary regimens include doses of progestin product less than a dose equivalent to 2.5 mg of medroxyprogesterone acetate daily.--

At page 20, line 24, after "cancer." insert the following paragraphs:

—The term "estrogen product" as used herein includes ethinyl estradiol, mestranol (a 50 mg dosage of which is equivalent to 35 mg of ethinyl estradiol), conjugated equine estrogen,

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estrone, estradiol, esterified estrogens, estropipate, and other estrogen equivalents and estrogen agonists.

The term "effective for contraception" as used herein includes sufficient inhibition of fertility, including ovulation or implantation.

The term "contraceptive blood level" as used herein includes a blood level sufficient to inhibit fertility, including ovulation or implantation.--